REMARKS

Applicants request reexamination and reconsideration of the subject application pursuant to and consistent with 37 C.F.R. § 1.112 in light of the following:

STATUS OF CLAIMS

The status of the claims under examination has been misstated. Claims 1, 2, 8, 9, 11-14, 20, 21, 23-28, 32, 33, 35, 56, 57, 63, 64 and 66-98 remain in this application. Claims 13, 14, 20, 21, 23-28, 32, 33, 35 and 67-81 have been withdrawn from consideration as drawn to non-elected subject matter. Claims 1, 2, 8, 9, 11, 12, 56, 57, 63, 64, 66 and 82-98 are under examination. It is again pointed out that Claims 12 and 66 were not included in the previous rejection and are not included in the current rejection. Clarification is requested.

INFORMATION DISCLOSURE STATEMENT

Applicants appreciate the Examiner's consideration of the December 16, 2009 Information Disclosure Statement and the return of the initialed Form PTO-1449.

REJECTIONS WITHDRAWN

Applicants appreciate the Examiner's withdrawal of the previous 35 U.S.C. § 103(a) rejection.

CLAIM REJECTIONS - 35 U.S.C. § 103(a)

Claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 have been rejected as being unpatentable over Schultz et al. US 6194395 in view of Pitha US 4727064 and in view of Loftsson et al., J. Pharm. Sci., 2002, 91(11), pp. 2307-2316. Applicants believe that all of the claims under examination, that is, all of Claims 1, 2, 8, 9, 11, 12, 56, 57, 63, 64, 66 and 82-98 are patentable over this combination of references.

Applicants have previously established that, while Schultz et al. describe inclusion complex formation in solution to form injectable solutions, Schultz et al. describe solid formulations which are mixtures, not complexes, of cladribine and cylodextrin. Applicants have already shown, particularly with reference to the experiments described in the Van Axel Castelli et al. paper previously submitted, that

contrary to Schultz et al., the instantly claimed cladribine/cyclodextrin complex is not a simple mixture of the ingredients and has different properties from a mixture of cladribine and cyclodextrin. Therefore, the ratios of cladribine and cyclodextrin in Schultz et al.'s solid are irrelevant to the ratios of cladribine and cylodextrin in the presently claimed complexes. The fact remains that Schultz et al. only discloses complexes in solutions for injection, not for solid oral dosage forms.

Moreover, in making his rejection, the Examiner has taken a teaching of Schultz et al. completely out of context and from this he has constructed a rejection which is improper. Specifically, the Examiner states that Schultz et al. teach undesirable recrystallization of cladribine in tissue may occur and damage surrounding tissue (col. 2, lines 1-2), and on this teaching he builds his position about solid oral formulations of cladribine/cyclodextrin complexes. However, the passage in Schultz et al. relied upon by the Examiner needs to be read together with the preceding passages in col. 1., which clearly refers only to injectable formulations of high osmolality when injected by the subcutaneous route (sentence bridging columns 1 and 2 of Schultz et al.). The passage quoted has therefore no relation to solid oral dosage forms. After oral absorption, no crystallization in any tissue could or would occur. Thus, it cannot provide any motivation to one of ordinary skill to combine Schultz et al with the other cited references.

Nevertheless, Pitha US 4727064 has been cited in combination with Schultz et al. Indeed, Pitha was prior art cited during the examination of the Schultz et al. patent, as is evident from the fact that it is listed on the face of the Schultz et al. patent. The Pitha patent issued eleven years before the Schultz et al. application was filed and was clearly available to Schultz et al. at the time of the Schultz et al. invention. Nevertheless, Schultz et al. turned to inclusion complex formulation only as a way of providing suitable injectable formulations of cladribine. In contrast, for solid dosage forms they suggested simple mixtures. Moreover, Pitha did not even address cladribine as such, much less the fact that it is acid-labile and unstable in the acidic environment of the gastrointestinal system (Schultz et al., col. 1, lines 47-51). It is not seen how one of ordinary skill would be motivated to try to combine Pitha with Schultz et al. to provide an alternate solution for solid oral use.

Still further, since there is no mention of cladribine as such in Pitha, preparation of inclusion complexes disclosed therein of, for example, sex hormones (Example 4 in column 7) clearly uses conditions different from those used herein for cladribine.

With respect to the Loftsson et al. J. Pharm. Sci. literature article, applicants believe that the conclusions of the article have been taken out of context. Loftsson et al. do indeed describe particular situations in which self-association of cyclodextrin complexes may explain some observed solubilization phenomena. However, Loftsson et al. first studied the solubility of ibuprofen sodium salt, diflumisal sodium salt, alprazolam, 17β-estradiol and diethylstilbestrol in HPβCD. Then, aqueous HPβCD solutions, previously saturated with the sodium salts of either ibuprofen or diflunisal were saturated with a second drug (17β-estradiol, diethylstilbestrol or alprazolam). On page 2313, left column, first full paragraph, Loftsson et al. summarize their conclusions from these experiments:

> If the solubilization of a given drug (the first drug) is solely attributable to inclusion complex formation and if the slope of the obtained phase-solubility diagram is greater than unity, then it can be assumed that almost all cyclodextrin molecules in the aqueous complexation medium will be forming inclusion complexes with the drug. In this case, the concentration of free cyclodextrin in a saturated drug solution will be very low and under such conditions there will be very little capacity to solubilize a second water-insoluble drug in the same medium. Introduction of a second drug will then always result in some precipitation of the drug that previously was used to saturate the solution. However, if the first drug is partially solubilized through non-inclusion association, then there could be some capacity in the solution to solubilize the second drug in a similar manner as drugs are solubilized in micelles. In other words, with inclusion complexation, we will expect to see a consistent competitive effect between the first drug and the second drug, but if solubilization through non-inclusion association exists in the solution, we can expect to observe a cooperative effect, especially if the complexation efficacy of the second drug is low.

It is clear from the foregoing that Loftsson et al. were dealing with combinations of two drugs, one of which was negatively charged. Loftsson et al. do not mention cladribine or suggest both inclusion and non-inclusion association for it by itself in solid form. The presently claimed subject matter, a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex consisting of (a) an amorphous inclusion complex of cladribine with hydroxypropyl-β-cyclodextrin and (b) amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein, said composition having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16, is in no way suggested by the combination of references. See especially Claim 1 and Claim 56, drawn to the complex. Again, we emphasize that the ratios disclosed by Schultz et al. are for simple mixtures, not complexes. There is no reasonable evidence that any of the features of applicants' invention not taught by Schultz et al. are taught by the cited combination of references. Withdrawal of the record rejection is earnestly solicited.

In the event that any issues remain, the Examiner is urged to telephone the undersigned so that such issues can be handled promptly. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited. If the Examiner has no intention to allow the application, a personal interview with him and his supervisory Examiner is respectfully requested.

Respectfully submitted,

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